

Eczematous-type Multiple Drug Allergy From Isoniazid and Ethambutol With Positive Patch Test Results

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Practice Points

- Multiple drug allergy (MDA) from simultaneous use of antituberculosis drugs is a rare finding mainly presenting as an urticarial or maculopapular eruption.
- This report describes a case of eczematous-type MDA resulting from the novel combination of isoniazid and ethambutol that was confirmed by patch testing.
- Patch testing with graded concentrations of the drugs helped to exclude irritant patch test reactions.
- Dermatologists should consider the value of patch testing in determining the responsible agent in eczematous drug eruptions.

Multiple drug allergy (MDA) is characterized by hypersensitivity to 2 or more chemically unrelated drugs. Multiple drug allergy from simultaneous use of antituberculosis drugs is a rare phenomenon that mainly presents as an urticarial or maculopapular eruption. This case report describes a 58-year-old man who developed a generalized eczematous eruption during the sixth week of oral therapy with 4 antituberculosis drugs—isoniazid, ethambutol, rifampicin, and morphazinamide—for treatment of suspected pleural tuberculosis. The eruption resolved after treatment with systemic corticosteroids and cessation of isoniazid and ethambutol. During a lesion-free period 6 months after cessation of the corticosteroids, patch testing with serial dilutions of isoniazid and ethambutol revealed positive reactions; irritant patch test

reactions were excluded by testing with graded concentrations of each drug. The patient avoided the causative drugs and reported no new eruptions at 1-year follow-up. It is important for dermatologists to consider the value of patch testing in determining the causative drugs in suspected cases of eczematous-type MDA.

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Multiple drug allergy (MDA) from simultaneous use of antituberculosis drugs is a rare phenomenon mainly presenting as an urticarial or maculopapular eruption.^{1,2} This case report of eczematous-type MDA resulted from treatment with isoniazid and ethambutol hydrochloride that was confirmed by patch testing.

Case Report

A 58-year-old nonatopic man presented with a pruritic erythematous eruption of tiny vesicles on the trunk and extremities that developed during the sixth week of oral therapy with isoniazid, ethambutol, rifampicin, and morphazinamide hydrochloride, which had been started for treatment of suspected pleural tuberculosis. Histopathologic findings were

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consistent with an eczematous eruption. Ethambutol and morphazinamide were stopped, while isoniazid and rifampicin were continued; systemic corticosteroids also were administered, and the eruption partially regressed. Replacement of isoniazid with ethambutol worsened the eruption. Systemic corticosteroids could not be tapered off unless treatment continued with rifampicin only. During treatment with rifampicin and low-dose systemic corticosteroids only, the eruption resolved completely within 2 weeks. Systemic corticosteroids were tapered off and stopped over the following 2 weeks. The rifampicin also was stopped after 2 months because of

radiological and clinical disease regression as well as the risk for development of rifampicin resistance. A human immunodeficiency virus antibody test was negative. The patient's medical history revealed no prior use of antituberculosis drugs.

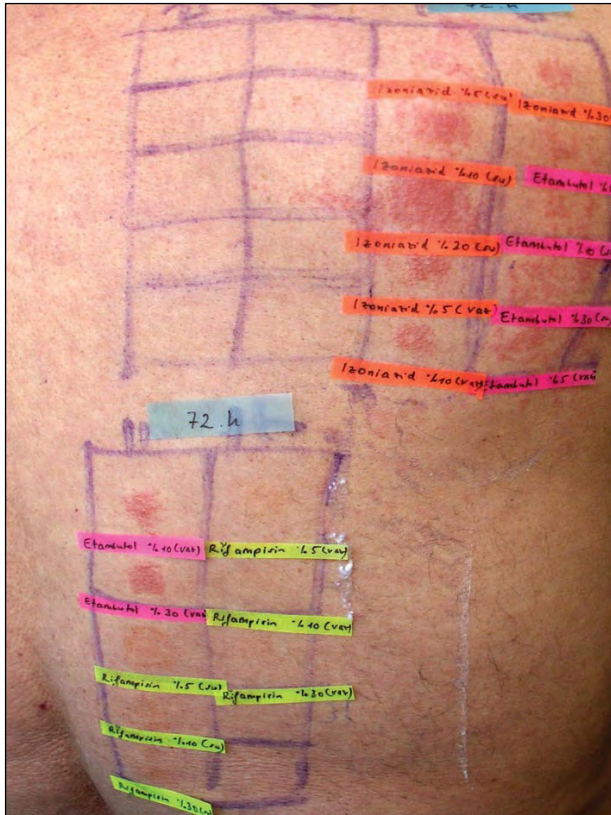
During a lesion-free period 6 months after cessation of the systemic corticosteroids, informed consent was obtained from the patient and patch testing was conducted. Topical application of serial dilutions of commercial formulations of isoniazid and ethambutol revealed positive reactions (Table)(Figure). The only active ingredients in the commercial products used were the antituberculosis agents, with

Patch Test Results With Serial Dilutions of Antituberculosis Drugs and the European Baseline Patch Test Series According to the International Contact Dermatitis Research Group Criteria^{3,a}

Patch Test Substance	Day 2	Day 3	Day 4
White petrolatum (negative control)	—	—	—
Isoniazid + vitamin B ₆ tablet 5% aq	Erythema	?+	++
Isoniazid + vitamin B ₆ tablet 10% aq	Erythema	+	++
Isoniazid + vitamin B ₆ tablet 30% aq	?+	++	+++
Isoniazid + vitamin B ₆ tablet 5% pet	++	++	++
Isoniazid + vitamin B ₆ tablet 10% pet	++	++	++
Isoniazid + vitamin B ₆ tablet 30% pet	++	++	++
Ethambutol hydrochloride tablet 5% aq	?+	+	+
Ethambutol tablet 10% aq	?+	+	+
Ethambutol tablet 30% aq	?+	++	++
Ethambutol tablet 5% pet	++	++	++
Ethambutol tablet 10% pet	++	++	+++
Ethambutol tablet 30% pet	++	++	+++
Rifampicin capsule 5%, 10%, and 30% aq and pet	—	—	—
European baseline patch test series	—	—	—

Abbreviations: aq, aqua; pet, petrolatum.

^aResults indicated — for negative reaction; ?+ for doubtful reaction; + for weak positive allergic reaction; ++ for strong positive allergic reaction; and +++ for extreme positive reaction.



Positive patch test reactions with serial dilutions of an isoniazid and vitamin B₆ tablet (isoniazid 5%, 10%, and 30% aqua and petrolatum) and ethambutol hydrochloride tablet (ethambutol 5%, 10%, and 30% aqua and petrolatum) at day 3.

the exception of one product containing isoniazid and vitamin B₆ (pyridoxine hydrochloride). Inactive ingredients were not available for patch testing. Oral challenge with a vitamin B₆ tablet (100 mg) was negative. Both drugs were assigned a score of 9 (definite adverse drug reaction) according to the Naranjo adverse drug reaction probability scale,⁴ which suggested a definite causal relationship between the drugs and the eruption in our patient.

Patch testing with graded concentrations of each drug helped to exclude the possibility of irritant patch test reactions. At a 1-year follow up, no further use of antituberculosis drugs was indicated and complete clearance of skin lesions was observed. Based on the clinical, histopathologic, and patch test findings in this patient, a diagnosis of eczematous-type MDA was made.

Comment

The terms *multiple drug allergy*, *multiple drug allergy syndrome*, and *multiple drug hypersensitivity* all have been used to describe the condition characterized by hypersensitivity to 2 or more chemically unrelated

drugs.⁵⁻⁷ The sensitization might develop simultaneously or sequentially.⁷ Immediate-type MDA is most frequently reported and typically presents with urticaria, angioedema, or anaphylaxis.^{5,6} Delayed-type MDA, predominantly presenting with a maculopapular or exanthematous eruption, rarely has been reported. A generalized eczematous eruption, as observed in the patient described here, seems to be an extremely rare clinical variant of delayed-type MDA.⁸

Antituberculosis drugs are rare inducers of MDA. In a large series of 3148 patients who received antituberculosis therapy, MDA was suspected in 0.3% of patients and mainly presented as a maculopapular or urticarial eruption resulting from streptomycin and para-aminosalicylic acid.¹ Development of delayed-type MDA that manifested as exfoliative dermatitis has been reported and confirmed via patch testing in 1 patient undergoing treatment with isoniazid and ethambutol.⁹ A case of a maculopapular eruption resulting from treatment with streptomycin, rifampicin, and ethambutol also has been reported.² Sequential development of MDA has been reported as a generalized eczematous eruption resulting from systemic use of streptomycin and again 13 years later from isoniazid; both instances were confirmed by patch testing.¹⁰

Isoniazid and ethambutol are known to cause contact dermatitis mainly from occupational exposure¹¹; however, eczematous eruptions resulting from systemic use are rare. The offending drugs in the patient presented here are not available in topical form, which suggests a primary systemic sensitization with drugs or their metabolites based on the concept of the pharmacologic interaction of drugs with immunoreceptors.¹²

Conclusion

This report describes a case of eczematous-type MDA resulting from the novel combination of isoniazid and ethambutol for the treatment of tuberculosis. Dermatologists should consider the value of patch testing in determining the responsible agent in eczematous drug eruptions.

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